REMARKS

Claims

Claims 2, 8, 10 and 13–17 are currently under examination with claims 11–12 withdrawn from consideration due to restriction/election and claims 1, 3–7 and 9 cancelled without prejudice or disclaimer.

Claim amendments

It is respectfully submitted that the claim amendments do not raise new matter. Entry thereof is earnestly solicited.

Claim objections and Rejections under 112, ¶2

Applicants appreciate the Examiner's careful reading of the claims. The foregoing amendments render these rejections moot.

Rejection under §112, ¶1

Claims 2, 8, 10 and 13–17 are rejected under this section as allegedly lacking written description of the antibody molecules and for allegedly failing to provide a disclosure of how to use such molecules in the claimed method(s).

Written Description

The court in Enzo Biochem v. Gen-Probe, Inc., 323 F.3d 956, 964 (Fed. Cir. 2002) ("Enzo Biochem II") establishes a legal precedent for written description of antibody molecules. The Enzo court adopted the USPTO Guidelines as persuasive authority for the proposition that a claim directed to "any antibody which is capable of binding to antigen X" would have sufficient support in a written description that disclosed "fully characterized antigens." Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/menu/written.pdf (Emphasis added). The decision in Enzo was later adopted in *Noelle v. Lederman*, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004). The *Noelle* court explicitly stated that the "disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen. (Emphasis added)" In view of the detailed disclosure in Applicants' own specification regarding the claimed antigen species (pro-HB-EGF), it is respectfully submitted that Applicant was in possession of the claimed antibody molecules as of the filing date of the present application. The specification provides explicit disclosure that the claimed molecules can be

used in a manner recited in the claims. See, for example, page 3, lines 8–21 of the originally-filed specification.

As for the consensus sequence in the pro-HB-EGF polypeptides, it is now well-settled that a specification need not disclose, and preferably omits, what is well known to those skilled in the art when an application is filed (for example, with respect to the sequence of pro-HB-EGF species). See, e.g., *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). See, also, MPEP §2164.05(a) and *Capon v. Eshhar v. Dudas*, (Fed. Cir. 2005) 418 F.3d 1349, 76 U.S.P.Q.2d 1078. A search on PUBMED with the term pro-HB-EGF discloses eight scientific articles, all of which were published before Applicants' earliest priority date (March 8, 2002). See, Exhibit A. Moreover, the Gen-Bank Accession number of a representative species of heparin-binding epidermal growth factor (human HB-EGF; M60278) is provided in Bevec et al. (WO 01/35899), which was cited in the Office Action dated January 9, 2008. See, page 14, lines 3–5 of WO 01/35899. Likewise, in the instant application, the specification need not provide express guidance with respect to the species of pro-HB-EGF. Withdrawal of the rejection is respectfully requested.

The following comments are further provided to rebut the contentions made in page 8 of the outstanding Office Action:

(a) Actual reduction to practice: As explicitly stated under MPEP §2138.05, "Reduction to practice may be an actual reduction or a constructive reduction to practice which occurs when a patent application on the claimed invention is filed. The filing of a patent application serves as conception and constructive reduction to practice of the subject matter described in the application. Thus the inventor need not provide evidence of either conception or actual reduction to practice when relying on the content of the patent application. Hyatt v. Boone, 146 F.3d 1348, 1352, 47 USPQ2d 1128, 1130 (Fed. Cir. 1998) (Emphasis added)." Withdrawal of this contention is respectfully requested.

(b) Identifying characteristics/Disclosure of drawings or chemical formulas: See, *Noelle v. Lederman*, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) and *Capon v. Eshhar v. Dudas*, 418 F.3d 1349, 76 U.S.P.Q.2d 1078 (Fed. Cir. 2005), discussed *supra*.

(c) Method of making an antibody: It is earnestly submitted that a skilled worker who is equipped with the claimed polypeptide species (for example, human pro-HB-EGF which is a polypeptide product of mRNA having GenBank Accession No. M60278) and who is

familiar with the techniques and/or reagents used in antibody engineering would possess a definitive understanding of what is described in Applicants' claims. Techniques for generating hybridomas, and use thereof, for example, in the production of immunologically reactive antibody molecules were well-appreciated before the filing date of the instant application. See, for example, the enclosed article by Kohler et al., (*Nature*, vol. 256; pp. 495-497, 1975). For example, the skilled worker could generate full-length antibody molecules having the immunospecificity and/or inhibitory activity recited in the present claims. Techniques of protein chemistry (for example, pepsin or trypsin digestion) could be used to generate other antibody species. Such methods are conventional. The Examiner is invited to review the reference by Mathews and Wells (*Science*, vol. 260, pages: 1113–1117, 1993), the abstract of which is enclosed herewith. Alternatively, the skilled worker could rely on recombinant techniques, for example, art knowledge of cloning and/or phage display libraries to rapidly generate antibodies. Screening techniques based on, for example, inhibition of processing of pro-HB-EGF, could be additionally utilized. See, *infra* with respect to the processing of pro-HB-EGF, as recited herein. The whole process constitutes nothing more than routineness.

(d) Level of skill in the art: Contrary to the Examiner's contention, the present specification provides a detailed disclosure of pro-HB-EGF processing. For example, the specification at page 3, lines 25–28 teaches that under one embodiment, "inhibition of the protease [of ADAM family] leads to a blocking of the processing of growth-factor receptor ligand precursors and thus results in an inhibition of growth-factor receptor activation." The specification at page 3, lines 9–11 teaches that the protease cleaves pro-HB-EGF to HB-EGF. As such, the specification provides adequate written description of the claim term "processing." Moreover, the term was well-appreciated in the art before the filing date of the present application. A search on PUBMED with the term "processing AND 'growth factor precursor'" identified more than 20 articles which were published before the earliest priority date. To this end, processing of heparin-binding epidermal growth factor precursor is described in Yu et al. Delsite et al. describe the processing of nerve growth factor precursor. See the enclosed Exhibit B and the review article by Seidah et al. (*Biochem J.*, 1996).

(e) Predictability: The Office Action contends that "it is not predictable that the antibody [that binds to pro-HB-EGF protein] would also inhibit processing of said pro-HG-EGF." It is unclear at how the PTO arrived at this contention. Absent adequate evidence to support

this assertion, the allegation and the rejection based thereon are both without legal merit.

As such, it is courteously submitted that these features are adequate to determine that applicant was in possession of the claimed invention. Noelle controls this case and establishes the existence of a written description. It is therefore courteously submitted that Applicants' claims in the current form, fully comply with the written description requirements under 35 U.S.C. § 112, ¶1, as specified in the PTO's own guidelines and the Federal Circuit. Withdrawal of the rejection is respectfully requested.

Finally, the Office Action at page 7, last paragraph alleges that "the specification does not otherwise cite a commercial example(s) of such antibody or reduce to practice any antibody meeting all these properties (i.e., binds pro-HB-EGF or blocks the processing thereof)." This contention is legally baseless. There is no requirement that Applicants provide commercial examples of antibody molecules.

Enablement

At the outset, it is respectfully submitted that in view of the amendment of the claims, the rejection under this section for allegedly failing to provide enablement of embodiments directed to the cancer preventive properties of the claimed antibody molecules is moot. Applicants' amendment of the claims is not to be construed with acquiescence to this or any other ground of rejection.

At page 9 of the Office Action, the rejection begins with a recitation of the so-called *Wands* factors. The Examiner asserts that these are the factors to consider when determining whether a disclosure satisfies the enablement requirement under 35 U.S.C. §112, ¶1. However, this is not an accurate description of the analysis of the *Wands* factors.

The Wands factors are to be used for determining whether undue experimentation is required for enablement. As expressly stated by the court in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, …" However, before the issue of undue experimentation arises, the rejection first must present reasons to doubt the veracity of the enablement statements presented in the specification.

Applicants' instant specification coupled with a skilled worker's knowledge provides adequate guidance to use the claimed molecules (for example, an antibody which binds to pro-HB-EGF and blocks the processing thereof) for practicing the claimed methods. The specification provides both general and specific guidance regarding the relationship between the activity of pro-

HB-EGF molecules with respect to the specific processes recited in the claims, for example, cell proliferation, cell migration, invasivity and/or anti-apoptosis. See, for example, the disclosure contained in the paragraph bridging pages 2 and 3 and page 3, lines 8–21 of the instant specification. Applicants' specification, for example, page 4, lines 18–20 expressly teaches that the claimed invention relates to treatment of cancer such as that of colon, kidney, liver, bladder, pancreas, prostate, GI, breast, lung, thyroid, pituitary, adrenal, ovarian or glial tissue. Using antibody molecules which bind to pro-HB-EGF as a representative example, the specification provides more than adequate guidance for the use of the claimed molecules in a manner that is described in the claims. Furthermore, the specification in view of the references cited therein conveys to one of ordinary skill in the art that pro-HB-EGF mediates tumorigenic effects both *in vitro* as well as *in vivo*. Applicants' specification teaches a number of ways via which such tumorigenic effects may be inhibited in the clinical setting. To this end, it is expressly taught that antibody-mediated binding and blocking of the processing of pro-HB-EGF molecules neutralizes the effect thereof *in vivo*. . See, for example, page 3, lines 8–21 of the originally-filed specification.

As clearly and succinctly stated by the court in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> As a matter of Patent Office practice, then a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken in compliance with the enabling requirement of the first paragraph of §112, **unless** there is reason to doubt the objective truth of statements contained therein relied on for enabling support. (emphasis in original)

See also, for example, *In re Brana, 51 F.3d 1560,* 34 USPQ2d 1436 (Fed. Cir. 1995), and *Fiers v. Revel, 984 F.2d 1164,* 24 USPQ2d 1601 (Fed. Cir. 1993). Furthermore, as stated in *Marzocchi*, at 370, the PTO must have adequate support (evidence or reasoning) for its challenge to the credibility of applicants' statements of utility. See also *In re Bundy*, 209 USPQ 48 (CPA 1981). Thus, in the absence of evidence which demonstrates otherwise, the claims must be taken to satisfy the requirements of 35 U.S.C. § 112, ¶1. Here the contention is regarding the use of antibody molecules having the claimed structural (i.e., binding to a well-characterized pro-HB-EGF protein) and functional (i.e., blocking the processing thereof) features can be utilized in a manner recited in the claims.

In light of this detailed disclosure, the courts have placed the burden on the PTO to show otherwise. It is courteously submitted that the Examiner has not presented any evidence to refute the findings or the conclusions made in the specification or the supporting publications.

The contention that Applicants' specification provide working examples to comply with the enablement requirements under §112, ¶1 is respectfully traversed. As stated by the court *Marzocchi*, 169 U.S.P.Q. 367, 369 (CCPA 1971) at 369:

> The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

The MPEP further states that "compliance with the enablement requirement of 35 U.S.C. 112, ¶1, does not turn on whether an example is disclosed." See MPEP § 2164.02. Withdrawal of the contention is respectfully requested.

Moreover, enablement is viewed in the context of what one or ordinary skill in the art knows, and such persons of ordinary skill in the art, for example, can make the claimed antibody molecules based on, for example, the disclosure contained in Appellants' own specification and the reference publications on antibody engineering. See, for example, *Spectra-Physics v Coherent*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987). See also *Amgen v Hoechst Marion Roussel*, 65 USPQ2d 1385 (CA FC 2003) holding that the "specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation.'" As such, the PTO's contentions are especially weak in the face of the showing that the scientific knowledge pertaining to the use of antibody molecules that bind to growth factor receptor ligands (for example, EGF, PDGF, Her2, etc.) was mature prior to the filing date of the instant application. To this end, the Examiner is cordially requested to review the disclosure contained in enclosed publications.

Molina (*Cancer Research*, 2001) describes the ability of therapeutically effective antibody Trastuzumab, which binds selectively with high affinity to the extracellular domain of Her2, to inhibit the cleavage of the extracellular domain of the receptor tyrosine kinase Her2 *in vitro*. The therapeutic antibody has now been utilized for the treatment of tumor patients. See, the disclosure contained Table 1 and Table 2 of the enclosed product brochure on Trastuzumab. These disclosures demonstrate the credibility of the disclosures of the application and demonstrate it is not reasonable to doubt their veracity.

In view of the above remarks, Appellants submit that the instant disclosure objectively enables one of ordinary skill in the art to make and use the claimed invention with an effort that is routine within the art. The lack of enablement rejection is misplaced and withdrawal thereof is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Encl.

(a) Exhibits A and B
(b) Non-patent literature references
(c) PTO-1449